a2 cont

30. (New) The method of claim 29, wherein said monoclonal antibodies comprise antibodies having an affinity constant of greater than 1×10^5 liters per mole for said antigen.

REMARKS

Status of Claims

Claims 1-13 are pending in the instant application and have been examined. Claims 1-13 stand rejected under 35 U.S.C. §112, first paragraph. Claims 1, 7, 8 and 13 stand rejected under 35 U.S.C. §112, second paragraph. Claims 1-4, 6-10, 12 and 13 stand rejected under 35 U.S.C. §102(b) as anticipated by the Hammerling et al. journal article. Claims 1, 3, 4, 6 and 7 also stand rejected under 35 U.S.C. §102(b) as anticipated by the PCT publication WO 96/14401. An objection to the specification has been presented. Claims 5 and 11 are indicated to be "free of cited prior art of record because the cited prior art of record fails to teach using a CD19 transgenic mouse line to facilitate monoclonal antibody production." Official Action, page 8.

Claims 1 and 2 have been amended. Claims 29 and 30 have been added. Claims 6 and 8-13 have been cancelled. No new matter has been added. Support for the amendments made to claim 1 and 2 can be found throughout the specification, notably on page 8, lines 16-17 and in Figure 3; page 9, lines 17-24; page 10, line 3 to 26; and the in Laboratory Examples, particularly Laboratory Example 1 (see, e.g., page 21, line 26 through page 22, line 15; page 30, lines 8-13 and lines 29-31), Laboratory Example 2 (see, e.g., page 38, lines 10-12) and Laboratory Example 3 (see, e.g., Table 2 and page 48, lines 22-27). Claims 29 and 30 are drawn to material identified by the U.S. Patent and Trademark Office (hereinafter the "Patent Office") as free of the cited prior art of record and are supported by the specification as filed.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made**." Deletions are bracketed and additions are underlined.

Reconsideration of the application as amended and based on the arguments set forth herein below is respectfully requested.

Response to the Objection to the Specification

The Patent Office has objected to the specification for reasons set forth in detail on page 2 of the Official Action. Specifically, the Patent Office states that the specification does not comply with the Sequence Listing requirements of 37 CFR 1.821(a)(1) and (a)(2). The Patent Office states, "the paper copy is in the old format and the CFR is in the new format. Applicant must resolve the contradiction in sequence listing by providing a substitute paper copy of the Sequence Listing and a new statement that the content of the paper and computer readable copies are the same, and where applicable, include no new matter." Official Action, page 2.

Applicant submits herewith a new CRF, a paper copy of the Sequence Listing corresponding to the new CRF and a statement that the content of the paper and computer readable copies are the same. Please replace the Sequence Listing in the application as filed with the new Sequence Listing, submitted herewith. A statement that the content of the CRF and the paper copy are identical is also submitted herewith.

Response to the Rejection of the Claims Under

35 U.S.C. §112, First Paragraph

Claims 1-13 have been rejected by the Patent Office under 35 U.S.C. §112, first paragraph, for the reasons set forth in detail at pages 3-5 of the Office Action. It is the Patent Office's position that "the specification does not provide an adequate disclosure to all molecules that would alter antibody production, and all possible methods of cellular manipulation." Official Action, page 3. The Patent Office then characterizes the claimed subject matter as a genus of cells encompassing "any cell that producing [sic] antibodies, not possible in unmanipulated controls or in an increased quantity and/or facilitated process compared with unmanipulated controls." Official Action, page 4. The Patent Office then asserts, "the disclosed CD19-CD21 pathway is not a representative species of the genus." Official Action, page 4.

Summarily, the Patent Office contends:

> [A] skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of any and all cells having a manipulated characteristic or a disrupted peripheral tolerance. Therefore only the described CD19 transgene manipulation meets the written description provision of 35 U.S.C. § 112, first paragraph.

Official Action, page 5. Applicant respectfully traverses the rejection and submits the following comments.

As a matter of Patent Office practice, the burden rests upon the Patent Office to establish a prima facie case of a failure to comply with 35 U.S.C. § 112, first paragraph, with respect to the invention described and claimed in applicant's patent application. See In re Marzocchi, 58 C.C.P.A. 1069, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971).

The Patent Office contends that the specification of the present U.S. patent application does not show that applicant was in possession of the claimed invention commensurate to the scope of the claims. However, no specific scientific or other factual basis in support of this contention has been presented in the Official Action. Indeed, the two journal articles offered by the Patent Office in support of its position (Strasser et al. and Yoshino et al.) are characterized in general terms and do not support the specific contentions the Patent Office has made.

Applicant submits that the Patent Office has not met its burden, as is required under In re Marzocci. Rather, the Patent Office has offered only a series of conclusory statements, contending generally that the specification of the present patent application "does not provide adequate written description for the broad class of any and all cells having a manipulated characteristic or a disrupted peripheral tolerance." Official Action, page 5. Applicant respectfully submits that a prima facie case under 35 U.S.C. §112, first paragraph, has not been made.

Indeed, 35 U.S.C. §112, first paragraph, requires no more than a disclosure sufficient to convey to one of ordinary skill in the art that applicant was in possession of the invention commensurate with the scope of the claims, and this requirement has clearly been met. Accordingly, claims 1-5 and 7 are believed to be in compliance with 35 U.S.C. §112, first paragraph. Withdrawal of this rejection of claims 1-5 and 7

is respectfully requested.

However, assuming arguendo that, based on the two general references cited, the Patent Office has made a prima facie case of a failure to comply with 35 U.S.C. §112, first paragraph, applicant respectfully submits the following. The Patent Office's primary contention in support of the rejection under 35 U.S.C. §112, first paragraph, appears to be that the specification "does not provide adequate written description for the broad class of *any* and *all* cells having a manipulated characteristic or a disrupted peripheral tolerance." Official Action, page 5.

Claim 6 has been cancelled. Claim 1 now recites B lymphocytes exhibiting a transmembrane signal transduction response of a degree not observed in conventional B lymphocytes. Support for this amendment can be found throughout the specification, as noted herein above. Applicant further notes that at least Laboratory Examples 1 and 3 disclose specific guidance for the immunization of an animal having B lymphocytes exhibiting a transmembrane signal transduction response of a degree not observed in conventional B lymphocytes. Specifically, Laboratory Example 1 discloses procedures for producing monoclonals to an antigen. Specific animal lines are also disclosed (e.g., hCD19). Specific conditions for forming a hybridoma are known in the art and are incorporated by reference in the specification (i.e., G. Kohler and C. Milstein (1975) *Nature* 256: 495-497; (1976), *Eur. J. Immunol.* 6: 511-519, recited on page 3 of the specification). See also Table 2 of Laboratory Example 3.

Claim 2 has been amended to recite the element that the transmembrane signal transduction response is accompanied by disrupted peripheral tolerance. Claims 2-5 and 7 depend directly or indirectly from claim 1 and incorporate the limitations of the claim from which they depend.

Applicant submits that amended claims 1 and 2, and dependent claims 3-5 and 7 recite subject matter described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Indeed, the C.A.F.C. has held: "If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if not

every nuance of the claims is explicitly described in the specification, then the adequate written description requirement is met." In re Alton, 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996). Applicant submits that amended claim 1 now recites a cell type, namely B lymphocytes. Additionally, amended claim 1 recites a characteristic of the B lymphocytes, namely exhibition of a transmembrane signal transduction response of a degree not observed in conventional B lymphocytes. Both the named cell type and the recited characteristic are supported in the specification. Applicant submits that one of ordinary skill in the art would recognize that the inventor was in possession of the invention, and that the written description requirement of 35 U.S.C. §112, first paragraph is satisfied.

As the court stated in Vas-Cath, Inc. v. Mahurkar: "[T]he application must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*." Vas-Cath, Inc. v. Mahurkar, 19 U.S.P.Q.2d 111, 1117 (Fed. Cir. 1991) (emphasis in original). Applicant submits that the invention that is currently claimed is amply described in the specification of the present application, as well as in the Laboratory Examples disclosed therein.

Applicant further points out that the written description requirement of 35 U.S.C. §112, first paragraph is not meant to substitute for enablement. The fundamental purpose of the written description requirement of 35 U.S.C. §112 was succinctly stated by the United States Court of Customs and Patent Appeals:

> Acknowledgement of [the written description] requirement evidences appreciation of an important purpose of §112, first paragraph, which is the definition of the attributes which a patent specification must possess as of the filing date to be entitled to that filing date as a prima facie date of invention. Satisfaction of the description requirement insures that subject matter presented in the form of a claim subsequent to the filing date of the application was sufficiently disclosed at the time of filing so that the prima facie date of invention can fairly be held to be the filing date of the application.

Application of Samuel Smith and Allen J. Hubin, 481 F.2d 910, 914, 178 USPQ 620, 623 (C.C.P.A. 1973). This court further held: "Where the claim is an original claim, the underlying concept of insuring disclosure as of the filing date is satisfied, and the description requirement has likewise been held to be satisfied." Id. at 624.

Summarily, the written description requirement is satisfied by the original claims themselves. This point has been stressed by the courts since 1973:

> But we see no need for either additional representative examples or more definite language to satisfy the description requirement. Claim 2, which apparently was an original claim, in itself constituted a description in the original disclosure equivalent in scope and identical in language to the total subject matter now being claimed. See In re Anderson, 471 F.2d 1237 (C.C.P.A. 1973). Nothing more is necessary for compliance with the description requirement of the first paragraph of 35 U.S.C. § 112.

In re Gardner, 475 F.2d 1389, 1391, 177 U.S.P.Q. 396, 397 (C.C.P.A. 1973).

Turning now to the Examiner's rejection of claims 1-13, applicant notes that these claims are *original* claims. Applying the principles articulated by the long standing case law presented above, applicant submits that the rejection of these claims under 35 U.S.C. §112 is improper. Applicant submits that written description requirement has been met by the claims and specification of the application as filed.

Applicant submits that in view of the above remarks, claims 1-4 and 7 are in compliance with 35 U.S.C. §112, first paragraph. Based on the above comments, applicant therefore respectfully requests that the rejection of claims 1-4 and 7 under 35 U.S.C. §112, first paragraph be withdrawn. Allowance of claims 1-4 and 7 is also respectfully requested.

Response to the Rejection of the Claims Under

35 U.S.C. §112, Second Paragraph

Claims 1, 7, 8 and 13 have been rejected by the Patent Office under 35 U.S.C. §112, second paragraph, for the reasons set forth in detail at page 5 of the Official Action. It is the Patent Office's position that these claims are vague and indefinite because the claims recite the term "high affinity." The Patent Office contends "[t]he specification does not definite the term and fails to provide a standard for ascertaining the reqisit degree of the high affinity, and one of skill in the art would not be reasonable apprised of the scope of the invention." Official Action, page 5. Applicant respectfully traverses the rejection and submits the following comments.

Claims 8 and 13 have been cancelled. Applicant directs attention to page 41, lines 5-24 of the application as filed. This section explicitly defines the term "high

affinity." At one point, the specification states, "[t]he term 'high affinity' refers to a particular good fit of an antigenic determinant to a single antigen-binding site. Specification, page 41, lines 8-9. The specification further states, "[a] high affinity antigen-antibody interaction is therefore typically described as having an affinity constant K of greater than 1 x 10^5 liters per mole." Specification, page 41, lines 21-23. Applicant therefore submits that contrary to the Patent Office's contention, the term "high affinity" is clearly defined in the specification and is not vague or indefinite.

Applicant additionally notes that claim 1 does not recite the term "high affinity." A claim cannot be rejected for indefiniteness in a term it does not contain. Although claim 7 contains the term "high affinity," this claim depends from claim 1, which does not. Thus, dependent claim 7 incorporates additional claim elements not found in claim 1, including the term "high affinity" which is absent from claim 1.

Applicant submits that in view of the above remarks, claims 1 and 7 are in compliance with 35 U.S.C. § 112, second paragraph. Based on the above comments, applicant therefore respectfully requests that the rejection of claims 1 and 7 under 35 U.S.C. § 112, second paragraph, be withdrawn. Allowance of claims 1 and 7 is also respectfully requested.

Response to the Rejection of the Claims Under 35 U.S.C. §102(b)

in View of the Hämmerling et al. Journal Article

The Patent Office has rejected claims 1-4, 6-10, 12 and 13 under 35 U.S.C. §102(b) as being anticipated by the Hämmerling et al. journal article (hereinafter the "Hämmerling et al." journal article). The Patent Office contends:

> Hämmerling et al. teach a method for production of monoclonal antibodies having narrow specificity for polymorphic HLA alloantigens, comprising the step of immunizing a HLA-transgenic mice line having self-tolerance (a disrupted peripheral tolerance) to a particular HLA molecule, with skin grafts and lymphoid cells (antigen) of a second HLA-transgenic mouse expressing a different HLA molecule, such that a specific immune respose to a particular allelic HLA difference between donor and recipient transgenic mice is elicited.

Official Action, page 6. The Patent Office further contends: "The method taught by Hämmerling et al. facilitates specific anti-HLA alloantigen monoclonal antibody production, thus, Hämmerling et al. anticipate the instant claims." Official Action,

page 7. Applicant respectfully traverses the rejection and submits the following comments.

Applicant initially notes that claims 6 and 8-13 have been cancelled. Thus, the following remarks are directed to claim 1-5 and 7. In order for the Hämmerling et al. journal article to be an anticipating reference under 35 U.S.C. §102(b) the reference must disclose each and every element of the claimed invention. "[A]nticipation under §102 can be found only when the reference discloses exactly what is claimed and that where there are differences between the reference disclosure and the claim, the rejection must be based on §103 which takes differences into account." Titanium Metals Corp. v. Banner, 778 F.2d 775, 780, 227 U.S.P.Q. 773, 777 (Fed. Cir. 1985) citing D. Chisum, Patents § 3.02. The Hämmerling et al. journal article does not disclose each and every element of the presently claimed invention and therefore does not anticipate the presently claimed invention.

The Patent Office characterizes the Hämmerling et al. journal article as disclosing "a method for production of monoclonal antibodies having narrow specificity for polymorphic HLA alloantigens." Official Action, page 6. The Patent Office further characterizes the method of Hämmerling et al. journal article as comprising the step of immunizing a HLA-transgenic mice line having self-tolerance (a disrupted peripheral tolerance) to a particular HLA molecule." Official Action, page 6.

The Hämmerling et al. journal article is asserted to disclose a method of generating antibodies to an alloantigen. The reference is also asserted to disclose generating a transgenic animal by inserting HLA class I genes into its genome. The animal then expresses the HLA genes and develops a tolerance for these expression products. Subsequently, the animal is challenged by immunizing the animal with a tissue comprising cells expressing a different HLA allotype from the allotype of the HLA transgene. The animal is seen to mount an immunological response to the challenge. Unlike the Hämmerling et al. journal article, the present invention is not focused on generating a transgenic animal expressing a first foreign protein, to which it develops tolerance. Nor is the present invention focused on generating antibodies of narrow specificity in response to a challenge from an antigen comprising an

allotype different from the allotype of the transgene. Instead, the present invention is directed to the production of monoclonal antibodies formed as a result of a transmembrane signal transduction response of a degree not observed in conventional B lymphocytes, as reflected in amended claim 1.

Claim 1 recites immunizing an animal having B lymphocytes exhibiting a transmembrane signal transduction response of a degree not observed in conventional B lymphocytes, with an antigen to permit said B lymphocytes to produce antibodies to the antigen. The Hämmerling et al. journal article does not disclose a subject having B lymphocytes exhibiting a transmembrane signal transduction response of a degree not observed in conventional B lymphocytes.

Summarily, the Hämmerling et al. journal article addresses an entirely different problem than that solved by the present invention. Indeed, the present invention does not claim or disclose the generation of antibodies of narrow specificity formed in response to a challenge by an antigen comprising an allotype different from an allotype of a transgene. Instead, the present invention pertains to the problem of producing antibodies in a system comprising B lymphocytes exhibiting a transmembrane signal transduction response of a degree not observed in conventional B lymphocytes.

Applicant submits that the Hämmerling et al. journal article does not describe each and every element of the present invention and therefore does not anticipate the claims. Specifically, the Hämmerling et al. journal article does not describe immunizing an animal having B lymphocytes exhibiting a transmembrane signal transduction response of a degree not observed in conventional B lymphocytes. Claims 6 and 8-13 have been cancelled. Claims 2-4 and 7 are dependent on patentably distinguished claim 1. Applicant therefore respectfully requests that the rejection of claim 1-4 and 7 under 35 U.S.C. §102(b) be withdrawn. Allowance of claims 1-4 and 7 is also respectfully requested.

Response to the Rejection of the Claims Under 35 U.S.C. §102(b)

in View of PCT Publication WO 96/14401

The Patent Office has rejected claims 1, 3, 4, 6 and 7 under 35 U.S.C. §102(b) as being anticipated by the PCT Publication WO 96/14401 (hereinafter "PCT publication WO 96/14401"). The Patent Office contends: "WO9614401 teaches a method for monoclonal antibody production comprising the step of immunizing a transgenic animal with an antigen, wherein the lymphocytes of the transgenic animal contain genetic material which confers a selectable phenotype there on (a manipulated characteristic)." Official Action, page 7. PCT Publication WO 96/14401 does not disclose or claim an a method of producing antibodies in a system comprising B lymphocytes exhibiting a transmembrane signal transduction response of a degree not observed in conventional B lymphocytes.

PCT Publication WO 96/14401 is asserted to disclose the generation of a transgenic animal, wherein the transgene comprises a selectable phenotype, which can be employed in screening protocols. PCT Publication WO 96/14401 states, "The present invention provides transgenic organisms which inter alia constitute a very convenient source of material for the isolation, identification, culture and analysis of cells from any tissue of the organism's body." PCT Publication WO 96/14401, page 8, lines 17-20. PCT Publication WO 96/14401 further states,

> According to one aspect of the present invention, there is provided a transgenic eukaryotic organism having cells containing heterologous DNA comprising a transgene encoding a positive selectable marker and a transgene encoding a negative selectable marker. But for the selectable phenotypes arising from the transgenes, the organism may be essentially normal, the transgenes for example not being located such that they insertionally inactivate a gene.

PCT Publication WO 96/14401, page 9, lines 3-11. Thus, PCT publication WO 96/14401 is clearly focused on the generation of transgenic organisms expressing a selectable phenotype.

The present invention does not claim or disclose the notion of a selectable phenotype. Instead, the present invention is directed to producing antibodies in a system comprising B lymphocytes exhibiting a transmembrane signal transduction response of a degree not observed in conventional B lymphocytes. The specification of the present patent application does not claim or even mention employing a

selectable phenotype encoded by a transgene. Thus, PCT Publication WO 96/14401 attempts to address the problem of generating transgenic organisms expressing a selectable phenotype, which is an entirely different problem from the problem addressed by the present invention, namely producing antibodies in a system comprising B lymphocytes exhibiting a transmembrane signal transduction response of a degree not observed in conventional B lymphocytes.

Applicant submits that PCT Publication WO 96/14401 does not describe each and every element of the present invention and therefore does not anticipate claim 1, nor does it anticipate claims 3, 4, or 7, which depend from claim 1. Claim 6 has been cancelled. Applicant therefore respectfully requests that the rejection of claims 1, 3, 4 and 7 under 35 U.S.C. §102(b) be withdrawn. Allowance of claims 1, 3, 4 and 7 is also respectfully requested.

New Claims 29 and 30

New claims 29 and 30 have been added. Claims 29 and 30 do not embody any new matter. Support for new claims 29 and 30 can be found throughout the application as filed, notably on page 10, Lines 10-11 and in Laboratory Example 1. As noted above, claims 29 and 30 are directed to subject matter indicated by the Patent Office to be free of the prior art. Accordingly, allowance of claims 29 and 30 is respectfully requested.

CONCLUSIONS

In light of the above amendments and remarks, applicant submits that the subject patent application is in condition for allowance and courteously solicits a Notice of Allowance.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

Although it is believed that no fee is due, the Commissioner is hereby authorized to charge any deficiencies of payment associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS & WILSON, P.A.

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Enclosures

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PATENT TRADEMARK OFFICE

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 1 and 2 have been amended as follows:

1. (Amended) A method for production of a monoclonal antibody to an antigen comprising:

(a) immunizing an animal[,] having B lymphocytes [antibody-producing cells] exhibiting a transmembrane signal transduction response of a degree not observed in conventional B lymphocytes, [with a manipulated characteristic that facilitates the antibody-producing cell's ability to produce antibodies,] with said antigen to permit said B lymphocytes [antibody-producing cells] to produce antibodies to said antigen;

(b) removing at least a portion of said antibody-producing cells from said animal;[,]

(c) forming a hybridoma by fusing one of said B lymphocytes [antibody-producing cells] with an immortalizing cell wherein said hybridoma is capable of producing a monoclonal antibody to said antigen;[,]

(d) propagating said hybridoma;[,] and

(e) harvesting the monoclonal antibodies produced by said hybridoma.

2. (Amended) The method of claim 1, wherein the transmembrane signal transduction response [said manipulated characteristic comprises] is accompanied by disrupted peripheral tolerance.

Claims 29 and 30 have been added:

29. (New) A method for producing a monoclonal antibody specific for an antigen, the method comprising:

(a) immunizing a transgenic mouse overexpressing CD19, and having antibody-producing cells with disrupted peripheral tolerance, with an antigen to permit said antibody-producing cells to produce antibodies to the antigen;

(b) removing at least a portion of said antibody-producing cells from the mouse;

(c) forming a hybridoma by fusing one of the antibody-producing cells with an immortalizing cell wherein the hybridoma is capable of producing a monoclonal antibody to the antigen;

(d) propagating the hybridoma; and

(e) harvesting the monoclonal antibodies produced by the hybridoma.

30. (New) The method of claim 29, wherein said monoclonal antibodies produced comprise antibodies having an affinity constant of greater than 1×10^5 liters per mole for said antigen.